Pituitary Stalk Interruption Syndrome Revealed by Neonatal Cholestasis: Two Case Reports

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Abstract

Pituitary Stalk Interruption Syndrome (PSIS) is a rare congenital disorder causing multiple pituitary hormone deficiencies. Though neonatal cholestasis has various causes, PSIS is an uncommon and often overlooked etiology, likely linked to cortisol deficiency. We report two cases of neonatal cholestasis due to severe cortisol deficiency, highlighting the need to consider PSIS in differential diagnosis. We report two cases of a two-month-old female infant and a three-day-old male newborn presenting with neonatal cholestasis. Initial workups ruled out common infectious and metabolic causes. The association of hypoglycemia led to considering endocrine causes and tests revealed severe cortisol deficiency, with one case also exhibiting hypothyroidism. Brain MRI confirmed PSIS in both patients. Hormone replacement therapy with hydrocortisone, and levothyroxine when needed, led to resolution of cholestasis and stabilization of glucose levels. Follow-up showed persistent growth issues, prompting growth hormone (GH) therapy initiation in one case, while GH testing was planned in the other. Neonatal cholestasis can be an early and often transient manifestation of PSIS, associated with cortisol deficiency. Early recognition and prompt hormone replacement therapy are essential for improving clinical outcomes. A comprehensive hormonal evaluation, including cortisol, thyroid, and GH levels, alongside pituitary MRI, is crucial for timely diagnosis and management.

Keywords: Cholestasis, Hypoglycemia, Pituitary Stalk Interruption Syndrome, Cortisol Deficiency.

Introduction

Pituitary Stalk Interruption Syndrome (PSIS) is a rare congenital disorder characterized by anatomic anomalies, including a hypoplastic anterior pituitary, an ectopic posterior pituitary, and an absent or interrupted pituitary stalk (1). Hormonal deficiencies in PSIS vary depending on the affected hormones and the timing of their onset. This syndrome presents with a range of clinical, biological, and imaging features, exhibiting significant heterogeneity and leading to a wide variety of manifestations among affected individuals (2). Cholestasis is a common symptom in neonates, with a broad spectrum of underlying etiologies. PSIS is a rare cause of neonatal cholestasis (3). Whether it involves single or multiple hormone deficiencies, the exact mechanism of liver dysfunction remains unclear. Here, we report two cases of severe cortisol deficiency presenting neonatal cholestasis.

Cases Report

Case one

A two-month-old female infant was admitted for progressive jaundice present since birth. She was born to healthy non-consanguineous parents after a full-term, uneventful pregnancy. Her growth and development were normal. On physical examination, the infant weighed 4.8 kg and had intense jaundice, with normal stool color and no hepatomegaly or splenomegaly.

Liver function tests showed elevated total serum bilirubin levels (180 mmol/L; conjugated fraction 111 mmol/L) and liver cytolysis: alanine aminotransferase (ALT) at 200 U/L and aspartate aminotransferase (AST) at

700 U/L. Gamma-glutamyl transpeptidase (GGT) activity was within normal limits at 13 U/L, and there was no evidence of liver failure (prothrombin time: 96%).

Initial investigations ruled out urinary tract infection and congenital infections, including syphilis, hepatitis, toxoplasmosis, rubella, and cytomegalovirus. Abdominal ultrasound revealed normal liver echotexture, normal bile ducts, and a well-visualized gallbladder.

On the third day of hospitalization, the infant developed generalized seizures triggered by severe hypoglycemia (0.13 g/L). Hypoglycemia was managed with intravenous glucose. While her condition improved, she required a glucose infusion rate of 10 mg/kg/min to maintain normal blood glucose levels.

The association of cholestasis and hypoglycemia without liver failure raised suspicion of an endocrine cause. Hormonal testing during a hypoglycemic episode confirmed hypocortisolemia (serum total cortisol: 134 nmol/L ; normal range: 250–650 nmol/L) with an adrenocorticotropic hormone (ACTH) level of 30 pg/mL (normal range: 7.2–63.3 pg/mL). Other hormone levels included normal thyroid-stimulating hormone (TSH) (1,59 mU/l ; normal range: 0,2-5 mU/l) and normal free T4 level (12,4 pmol/l ; normal range: 9-23 pmol/l). Intravenous hydrocortisone acetate was initiated, stabilizing blood glucose levels. Brain magnetic resonance imaging (MRI) revealed findings consistent with PSIS, with an ectopic posterior pituitary gland [Figure 1]. Hormone replacement therapy with oral cortisone acetate led to the resolution of jaundice and normalization of cholestasis markers within one month.

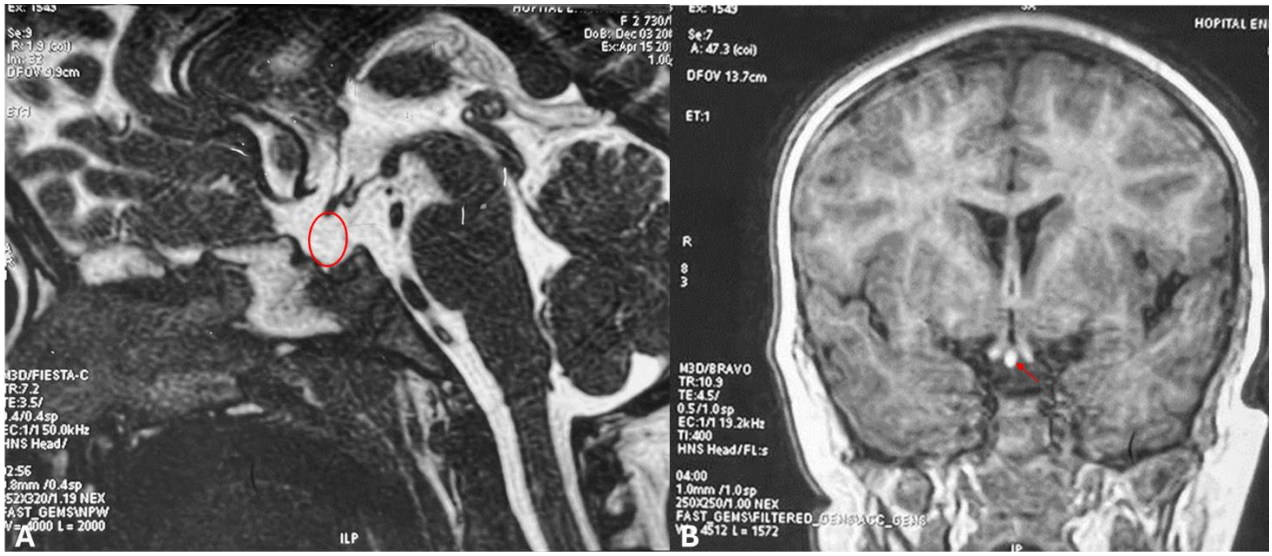

Figure 1: Brain magnetic resonance imaging **(a)** in sagittal section: 3D sequence heavily weighted in T2 revealing the absence of the pituitary stalk and hypoplasia of the anterior pituitary measuring 2.3 mm, **(b)** in coronal section T1 sequence revealing an ectopic posterior pituitary gland located at the median eminence with physiological hyperintense signal.

At two years of age, fellow-up showed a growth curve faltering. Investigations were conducted: no glucocorticoid overdose, normal thyroid function tests, and a GH stimulation test showing complete deficiency. The patient was started on GH replacement therapy, which resulted in significant improvement in growth. Currently, at 16 years of age, the patient has a height of 148 cm, a normal psychomotor development and normal thyroid function tests.

Case two

A male neonate, born at term to non-consanguineous parents, was admitted on the third day of life due to recurrent hypoglycemia. On clinical examination, he exhibited hypothermia, axial hypotonia, cholestatic jaundice, and normal stool color. He was hemodynamically stable and weighed 3.5 kg.

Persistent hypoglycemia necessitated a glucose intake of 12.5 mg/kg/min to maintain normoglycemia. An initial infection workup revealed a slightly elevated C-reactive protein of 7.2 mg/L, normal white blood cell count (6,910/mm^3), and negative blood cultures. Liver function tests showed cholestatic jaundice with total bilirubin of 162 mmol/L (conjugated fraction: 45.7 mmol/L), with normal levels of ALT (38.8 U/L) and AST (24.3 U/L), and significantly elevated GGT (409 U/L). An abdominal ultrasound revealed no abnormalities.

Infectious causes, hyperinsulinism, biliary atresia, and inherited metabolic disorders were systematically ruled out. The combination of cholestatic jaundice, elevated GGT, and hypoglycemia prompted hormonal evaluation. Cortisol levels were low (1.87 nmol/L; normal range: 170–540 nmol/L), while ACTH levels were within normal limits (44.37 pg/mL; normal range: 7.2–63.3 pg/mL). TSH levels were normal while free T4 level was low (8.1 pmol/l ; normal range: 9-23 pmol/l). Insulin-like growth factor-1 (IGF1) was low (IGF1<9.26 ng/ml, normal range: 49 – 171 ng/ml).

The diagnosis of corticotropic insufficiency and hypothyrpoidism was confirmed. The infant was initiated on hydrocortisone therapy and Levothyroxine, leading to clinical and biochemical improvement. Brain MRI revealed the absence of pituitary stalk with a hypoplastic anterior]pituitary and an ectopic posterior pituitary gland [Figure 2]. Cholestasis resolved with treatment within two weeks, with no recurrence of hypoglycemia. The patient is now 1 year old with balanced thyroid function tests and no signs of diabetes insipidus. However, his height remains below -2 standard deviations. A GH stimulation test is planned once the child reaches 10 kg, given the high risk of hypoglycemia.

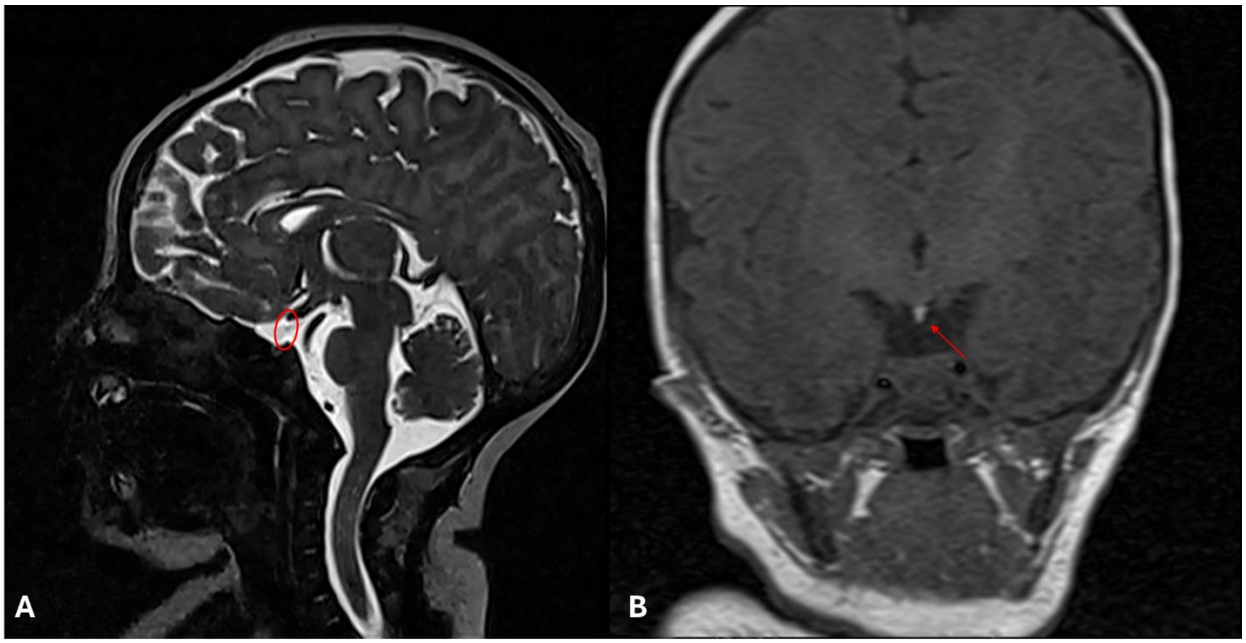

Figure 2: Brain magnetic resonance imaging **(a)** in sagittal section revealing the absence of the pituitary stalk, **(b)** in coronal section T1 sequence revealing an ectopic posterior pituitary gland.

Discussion

Congenital hypopituitarism should be considered an essential differential diagnosis in any infant presenting with cholestatic jaundice or unexplained hypoglycemia. PSIS, a rare congenital anomaly, often presents in the neonatal period with diverse clinical manifestations (2). Cholestasis has been reported in around 30% of cases across various series (2,4) and is often transient. It may sometimes be associated with risk factors for benign neonatal cholestasis, which can lead to the diagnosis being overlooked.

Patients with congenital hypopituitarism presenting with cholestasis can exhibit multiple pituitary hormone deficiencies, complicating the identification of the specific hormone responsible for liver dysfunction (5). Among pituitary hormones, cortisol, thyroid hormone, and GH play pivotal roles in bile acid synthesis and hepatobiliary system development. Their deficiencies likely contribute to impaired bile formation and excretion, as well as insufficient development of the biliary canalicular system (6). Moreover, in PSIS, hypoglycemia may be missed (2), highlighting the importance of systematically measuring cortisol levels in cases of neonatal cholestasis.

In our cases, cortisol deficiency emerged as the most critical factor contributing to the observed cholestasis. This finding aligns with previous studies that have highlighted the primary role of cortisol deficiency in such cases (2,7). Cortisol is essential for maintaining bile acid homeostasis and promoting hepatocyte function; its absence can lead to impaired bile secretion and cholestatic hepatitis. Moreover, the association of recurrent

hypoglycemic episodes with cholestasis, as seen in our patients, strongly supports cortisol deficiency as the underlying cause (7,8).

Diagnosis of PSIS and its related endocrine deficiencies requires a comprehensive hormonal work-up, including measurements of ACTH, cortisol, TSH, GH, and IGF-1, combined with MRI of the hypothalamic-pituitary region. Both patients in our report had classic MRI findings of pituitary stalk interruption with an ectopic posterior pituitary gland, confirming the diagnosis.

Management of PSIS involves hormone replacement therapy tailored to the patient's specific deficiencies. Treatment should begin with hydrocortisone to address cortisol deficiency. In case of hypothyroidism, thyroxine replacement is also critical to maintain normal growth and mental development. GH therapy is typically introduced later during infancy as the diagnosis is often made when growth curve falters (9). In cases of cholestasis, adjunctive therapies such as ursodeoxycholic acid and fat-soluble vitamins may support hepatic recovery (2).

While most cases of neonatal cholestasis associated with PSIS resolve with appropriate hormonal therapy, some reports describe poor outcomes, including cirrhosis and portal hypertension (10). Early recognition and intervention are thus paramount to improving prognosis. In our cases, prompt diagnosis and initiation of hormone replacement therapy led to the resolution of cholestasis and stabilization of glucose levels, underscoring the importance of timely management.

Conclusion

Neonatal cholestasis can be an initial manifestation of PSIS, although it is often transient. Timely recognition of cortisol deficiency, particularly when accompanied by hypoglycemia, is critical for prompt intervention and improved outcomes. Hormonal work-up combined with MRI of the hypothalamic-pituitary region are essential for diagnostic confirmation. Treatment involves hormone supplementation tailored to individual hormone deficiencies, alongside management of hepatic dysfunction.

Disclosure

No conflict of interest. The authors have no financial or proprietary interest in the subject matter of this article.

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Generative AI was used to review and correct spelling and grammar mistakes. The accuracy, validity, and appropriateness of the content were afterward verified by the authors.

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